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DNA-based catalytic enantioselective intermolecular oxa-Michael addition reactions†

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Using the DNA-based catalysis concept, a novel Cu(II) catalyzed enantioselective oxa-Michael addition of alcohols to enones is reported. Enantioselectivities of up to 86% were obtained. The presence of water is important for the reactivity, possibly by reverting unwanted side reactions such as 1,2-additions.

The catalytic enantioselective conjugate addition of alcohols, also known as the oxa-Michael reaction, is a reaction of great potential in organic synthesis.[1,2] Yet, the development of this reaction, and in particular the intermolecular variant, has been complicated by the inherently low reactivity of most alcohols in such reactions and the fact that the conjugate addition step is generally reversible. As a result, reports on catalytic enantioselective intermolecular oxa-Michael reactions of simple achiral alcohols to enones are scarce[5,6] and often involve alcohol analogues.[1–4] To date, up to 68% ee has been reported for organocatalytic intermolecular oxa-Michael additions of simple alcohols.[5] The intermolecular oxa-Michael addition has also been reported as the first step of a catalytic enantioselective tandem reaction, albeit that the enantioselectivity of the oxa-Michael step either was low or has not been determined separately.[7,8] Here we report on a novel Cu(II) catalyzed enantioselective oxa-Michael addition of alcohols to enones using the DNA-based catalysis concept.

In DNA-based catalysis, a hybrid catalyst is created by embedding a catalytically active non-chiral transition metal complex in duplex DNA.[9–12] Thus, the catalyzed reaction takes place in the chiral environment provided by the DNA helix resulting in enantioselective formation of the chiral reaction product. This concept has been applied successfully in a variety of catalytic reactions in water, in many cases giving rise to enantioselectivities > 90%.[13–16] Moreover, significant rate accelerations were observed for several of these reactions in the presence of DNA, which is attributed to favorable second coordination sphere interactions provided by the DNA scaffold.[9,17]

Recently, DNA-based catalysis was used to achieve the catalytic enantioselective *syn*-hydration of enones.[18] This remarkable reaction, which has no equivalent in homogeneous catalysis, suggested the possibility of achieving enantioselective intermolecular oxa-Michael addition of alcohols to enones.

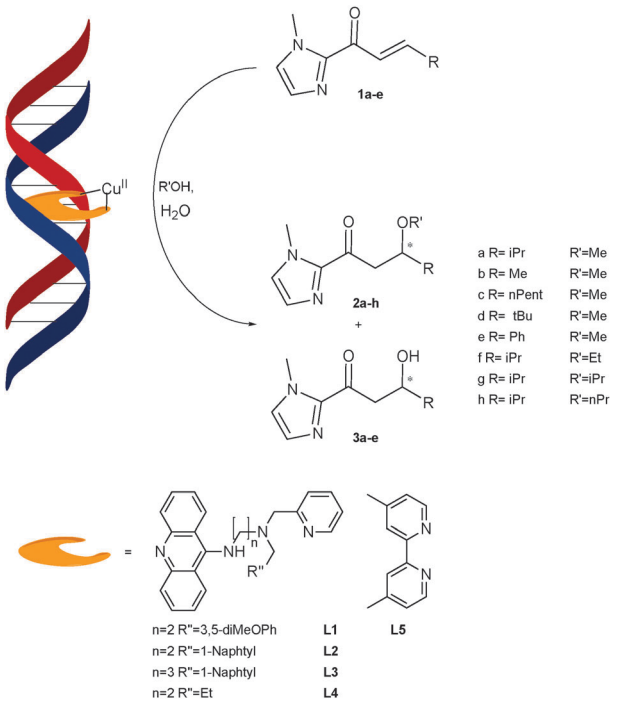

Fig. 1 DNA-based catalytic enantioselective intermolecular oxa-Michael addition reaction in water.

As a benchmark reaction the addition of methanol to α,β-unsaturated 2-acyl imidazole **1a** was investigated (Fig. 1). Since the DNA-based catalyst requires aqueous conditions, first the optimal water–methanol mixture was investigated in the reaction catalyzed by $Cu(NO_3)_2$ in the absence of DNA. Interestingly, it was observed that the highest yield of the methanol addition product **2a** was obtained when the catalyzed reaction was performed in a 50 : 50 water : methanol mixture; further increasing the fraction of methanol led to a lower yield of **2a** (Fig. S1, ESI†). This surprising observation suggests that water plays an important role in the reaction, possibly by reverting unwanted side reactions such as 1,2-additions of the alcohol, which would give rise to (hemi-)acetals. For the DNA-based reactions 40% v/v methanol was selected, since it was found before that this methanol content can be used without causing precipitation of DNA.[19]

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Table 1 Substrate and nucleophile scope

Entry	Substrate	R′OH	Ligand	Time	Conv.	Product	Ratio **2**:**3**	ee **2**	ee **3**
1	**1a**	MeOH	**L1**	4 h	82%	**2a**	59:41	64%	66%
2	**1a**	MeOH	**L2**	1 d	69%	**2a**	70:30	57%	59%
3	**1a**	MeOH	**L3**	1 d	34%	**2a**	58:42	4%	21%
4	**1a**	MeOH	**L4**	1 d	26%	**2a**	62:38	13%	46%
5	**1a**	MeOH	**L5**	1 d	28%	**2a**	54:46	−5%	5%
6[a]	**1a**	MeOH	**L1**	4 d	85%	**2a**	94:6	63%	66%
7	**1b**	MeOH	**L1**	4 h	Full	**2b**	87:13	24%	17%
8[a]	**1b**	MeOH	**L1**	1 d	Full	**2b**	99:1	25%	n.d.
9	**1c**	MeOH	**L1**	1 d	76%	**2c**	76:24	35%	51%
10[a]	**1c**	MeOH	**L1**	1 d	70%	**2c**	93:7	58%	82%
11	**1d**	MeOH	**L1**	4 d	43%	**2d**	58:42	81%	40% (*R*)
12[a]	**1d**	MeOH	**L1**	7 d	21%	**2d**	63:37	83%	85%
13	**1e**	MeOH	**L1**	1 d	—	**2e**	—	n.d.	n.d.
14	**1a**	EtOH	**L1**	11 d	74%	**2f**	51:49	52%	28%
15	**1a**	*i*-PrOH	**L1**	16 d	60%	**2g**	7:93	57%	36%
16	**1a**	*n*-PrOH	**L1**	11 d	65%	**2h**	32:68	86%	36%

Conditions: 0.66 mg ml^{-1} st-DNA, 20 mM MOPS pH 6.5, 0.165 mM **L1**, 0.15 mM $Cu(NO_3)_2$, 1 mM substrate, 40 v/v% R′OH, 4 °C.[a] Reaction performed at −18 °C. All conversions, product 2:3 ratios and enantioselectivities are the average of at least duplicate experiments; all values are reproducible within ±2%.

Bidentate nitrogen ligands L1–L5 were evaluated in the catalytic reaction in the presence of salmon testes DNA (st-DNA), which is inexpensive and readily available, at pH 6.5. This was determined to be the optimal pH with regard to enantioselectivity (Table S1, ESI†). In addition to the methanol addition product **2a**, ~30% of the hydration product **3a** was obtained as a side-product, with ee's similar to the methanol addition product. The highest enantioselectivities for the methanol addition product **2a** were achieved with the ligands **L1** and **L2**: 64% and 57% ee, respectively (Table 1; entries 1–5). This trend is consistent with what was observed before in the catalytic hydration reaction.[18] Since the highest conversions of **1a** were obtained with **L1**, this ligand was selected for further study.

Using Cu–L1/st-DNA and the optimized conditions, the substrate scope of the reaction was investigated. Several of these reactions were followed in time (Fig. S2–S4, ESI†) and the ee of the alcohol addition product **2** was found to be stable over time; no racemization occurred during the time investigated.[20] This is in contrast with the hydration product **3**, which in some instances does racemize.[18] It was found that the maximum conversion of the enone and the ratio of **2**:**3** decreased with increasing steric bulk of the substituent R at the β position (entries 1, 7, 9, 11, and 13). The opposite trend was observed for the ee of **2**, namely, an increase in enantioselectivity upon going from R = methyl (24% ee, entry 7) to R = *t*-butyl (81% ee; entry 11). In the case of R = phenyl, no conversion was observed. Most likely, the addition to this highly conjugated substrate is thermodynamically unfavorable.

The nucleophile scope was examined by using various alcohols (entries 14–16). It was found that the reaction rate decreased dramatically with increasing steric bulk of the alcohol. As a consequence also the ratio of **2**:**3** decreased. A clear illustration for this are the results obtained for the addition of iPrOH to **1a**: after 16 days 60% conversion of **1a** was achieved, of which only a minor fraction, *i.e.* 7%, was towards the alcohol addition product **2g** (entry 15). This indicates that *i*-propanol is too large to attack the β position of the enone and the hydration reaction becomes dominant. The highest ee for the alcohol addition product was obtained using *n*-propanol, that is, 86% (entry 16).

The reaction of **1a–d** with methanol was also performed at −18 °C, which is possible due to the high methanol content in the reaction mixture.[19] This resulted in a similar ee of the alcohol addition products, with exception of **2c** for which the ee increased from 35% to 58%. Interestingly, at −18 °C the hydration side reaction was suppressed. The ratio **2**:**3** was increased moderately in the case of **1d** (entry 12), but almost complete selectivity towards the alcohol addition product **2** was found for **1a–c** (entries 6, 8, and 10, Fig. S5, ESI†). Apparently, the rate of the hydration reaction depends much stronger on temperature than the alcohol addition reaction. Hence, even though the requirement for aqueous conditions causes the formation of a side product resulting from hydration of the enone, the reaction can be made chemoselective by lowering the reaction temperature.

A preliminary study of the DNA sequence dependence of the oxa-Michael addition, using self-complementary oligonucleotides as a catalyst scaffold, showed that duplexes containing a central AT segment give rise to higher ee's than duplexes with a central GC sequence (Table 2), a pattern that was also observed for the hydration reaction. However, the ee's obtained are lower than what is obtained with salmon testes DNA. This indicates that the optimal DNA sequence has most likely not been found to date. Additionally, it can also not be excluded that the high methanol content of the reaction mixture affects the structure and stability of small duplex DNAs and, hence, the enantioselectivity of the catalyzed reaction.[17]

Table 2 DNA-sequence dependence of the oxa-Michael addition of methanol to 1a

DNA sequence	Conv. (%)	Ratio **2**:**3**	ee **2a** (%)	ee **3a** (%)
TCAGGGCCCTGA	68	50:50	19	25
GCGCGCGCGCGC	71	58:42	14	31
GCGCTATAGCGC	85	53:47	36	40
CAAAAATTTTTG	82	40:60	43	39

Conditions: DNA (1 mM in bp), 20 mM MOPS pH 6.5, 0.165 mM **L1**, 0.15 mM $Cu(NO_3)_2$, 1 mM **1a**, 40 v/v% MeOH, 4 °C, 1 d.

In conclusion, using the DNA-based catalysis concept, we have achieved the catalytic enantioselective intermolecular oxa-Michael addition reactions of simple achiral alcohols to enones mediated by a transition metal complex in aqueous media. Up to 81% ee was achieved for the addition of methanol to enones and up to 86% ee could be obtained when using *n*-propanol as a nucleophile. These ee values represent the highest enantioselectivities achieved for the catalytic asymmetric intermolecular oxa-Michael addition reaction to date, thus illustrating the potential of the DNA-based catalysis concept.

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